

explains on page 1469 how  $FIC_{50}$  values were calculated and states that the calculations "can be represented graphically as isobolograms" (page 1469, second column). Several isobolograms are depicted in the Selleseth reference on pages 1469 and 1470.

Example 8 of the present application on page 20 describes the calculation of  $FIC_{50}$  values and their graphical representation as the isobologram of Fig. 1.

The Selleseth reference further explains on page 1469, second column, that "Datum points that fall significantly above the line representing dosewise additivity results from antagonism between the two drugs. Datum points that fall significantly below the line indicate synergy."

The datum points of Fig. 1 of the present application fall significantly below the line, indicating that the combination of the present invention is synergistic.

The isobologram representation is a widely accepted method of displaying combination drug effects as evidenced by the Selleseth reference and the references cited therein. Data points falling below the line joining the x and y axis (the zero interaction line), indicate that the two drugs are synergistic in their effect. Data points falling above the line indicate an antagonistic effect. Data points falling on the line indicate additivity.

The demonstration of the synergistic effect of the combination of the present invention is the demonstration of an unexpected effect. Therefore, since the combination of the present invention produces synergistic results, it is not obvious in view of Korba and Glazier alone or in combination. Applicants respectfully request withdrawal of the rejection of claims 1, 2, 4 - 10, 12 - 15, 22 and 23 under 35 U.S.C. § 103(a).

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In view of the foregoing discussion, it is respectfully submitted that the present application is in condition for allowance. An early consideration and notice of allowance are earnestly solicited.

Respectfully submitted,

Date: April 8, 2003

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